Perinatal and Long Term Outcome of Monochorionic Twins Complicated by Twin-Twin Transfusion Syndrome

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Abstract: Twin-twin transfusion syndrome (TTTS) is the most harmful complication of monochorionic twin pregnancies. Fetoscopic laser coagulation of placental vascular anastomoses represents the causative and first-line treatment for the disease. Substantial improvements in survival rates and long-term outcome have been achieved during the last 20 years of practice. This is due to improvements in antenatal detection of the condition, surgical skills and centralization in the referral fetal therapy unit, as well as postnatal intensive care and follow up programs. Major morbidity issues concern cardiologic, renal and cerebral functions and are mainly caused by intrauterine haemodynamic imbalances and prematurity. This review summarizes the current evidence on the prognosis of monochorionic twins survivors after TTTS treated by laser surgery, focusing on perinatal and long-term outcomes.

Keywords: Fetal therapy, High risk pregnancy, Neurodevelopmental impairment, Perinatal morbidity and mortality, Prematurity, Recipient twin cardiomyopathy, Twin pregnancy.

INTRODUCTION

Twin pregnancies are at increased risk of nearly all obstetric complications, but monochorionic diamniotic (MCDA) twin pregnancies show the highest risk of perinatal morbidity and mortality owing to the unique placental angioarchitecture [1-3].

Indeed, monochorionic twin pregnancies are characterized by the presence of vascular anastomoses between the circulations of both twins on the shared placenta [4,5]. There are three types of anastomoses: superficial artero-arterial (AA) and veno-venous (VV), with a bidirectional blood flow, and deep, artero-venous (AV), that allow unidirectional flow (Figure **1**). The difference in type, position and size of these anastomoses and the proportion of extension of each vascular territory, contributes to the development of typical complications of these pregnancies, including twin-twin transfusion syndrome (TTTS), selective intrauterine growth restriction (sIUGR), and twin anemia-polycytemia sequence (TAPS) [4, 5].

The current review aims to describe the actual prognosis of monochorionic twins after TTTS pointing at the state of the art of antenatal surgical treatment, fetal and neonatal morbidity and mortality as well as long-term health outcome of the survivors.

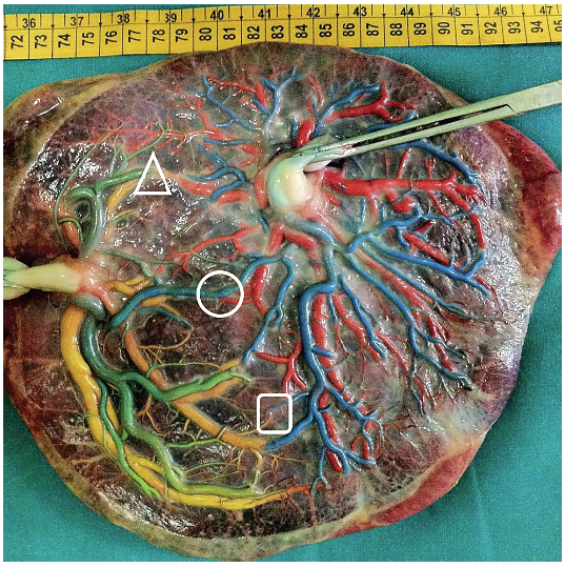

Figure 1: Monochorionic placenta from an uncomplicated MC twin pregnancy delivered at 36 weeks of gestational age. Injection study of the vascular anastomoses: in blue and green the arteries, in red and yellow the veins. Triangle: veno-venous anastomosis (yellow and red vessels); circle: artero-arterial anastomosis (green and blue vessels); square: artero-venous anastomosis (blue and yellow vessels).

TWIN-TWIN TRANSFUSION SYNDROME

TTTS is the best-known and most lethal complication of MC pregnancies, occurring in approximately 10% of cases [3]. Although the exact pathophysiology of TTTS is still unknown, the prevalent opinion is that it is caused by an imbalance in the blood exchange between one twin (the donor) and the other (the recipient) via placental anastomoses, due to a relative excess of unidirectional arterio-venous connections which is not compensated by reverse flow

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through other anastomoses. When a significant imbalance in blood flow occurs, the donor twin becomes hypovolemic and oliguric, develops severe oligohydramnios and signs of placental insufficiency. The recipient twin shows hypervolemia, polyuria and polyhydramnios, with cardiac overload, leading to hydrops in severe cases. These hemodynamic imbalances prompt an asymmetrical activation of the renin-angiotensin system between the twins which further worsen the pathogenic process of TTTS [6]. Without treatment, the prognosis is poor, with perinatal mortality in up to 100% of the cases. In survivors, severe preterm birth due to polyhydramnios is a major cause of neurologic morbidity [7].

The diagnosis of TTTS is only made by ultrasound following strict criteria standardized by the widespread staging system defined by Ruben Quintero in 1999, based on a polyhydramnios-oligohydramnios sequence (TOPS) and summarized in Table **1** [8]. The traditional neonatal criteria for diagnosing TTTS, based on an inter-twin hemoglobin difference (>5 g/100 mL) and birthweight discordance (>20%) do not apply in utero because similar discrepancies in hemoglobin and birthweight are also found in MC twins complicated by sIUGR and TAPS, without TTTS.

Antenatal follow up of MC twin gestations by biweekly ultrasounds from 16 weeks onwards is recommended by international guidelines in order to allow timely detection of TTTS [9]. In fact, early diagnosis of the condition and referral to a fetal therapy unit allows optimal management and improves the outcomes.

IN UTERO TREATMENT

In the past, serial amnioreduction (AR) was the most common treatment for TTTS [10]. Amnioreduction works by reducing the risk of preterm delivery secondary to uterine distension, and possibly also by relieving placental pressure allowing a reopening of compensatory vascular anastomoses. Endoscopic laser coagulation of placental anastomoses, a procedure first described by DeLia in the early 1990s, interrupts the vascular connections which are assumed to be responsible for the syndrome [11].

A randomized controlled multicentric trial which compared serial amnioreduction with laser coagulation have largely demonstrated that laser surgery is the best first-line treatment for TTTS diagnosed before 26 weeks, both in terms of perinatal survival and neurological outcome [12], while serial AR have been showed poor short and long-term outcome, with intrauterine survival rate usually below 60%, neonatal mortality up to 30% and long-term neurodevelopmental impairment in about 25% of the twins [13].

The laser procedure is performed with fetoscopy under local anesthesia. A 3 mm cannula is introduced in the amniotic sac of the recipient twin under ultrasound guidance using a percutaneous approach. A fiberscope is then passed through the cannula, so that the operator can explore the fetal surface of the placenta to identify the vascular connections and perform coagulation with a dedicated laser fiber. The intervention of laser coagulation usually ends with amniotic fluid drainage of the recipient sac till around normal levels.

The evidence of a postnatal persistence of anemia in one fetus and of polycythemia in the other despite the successful laser procedure, lead to the analysis of residual anastomosis and to identification of another type of complication, the twin anemia polycythemia sequence [14]. Post laser TAPS derives from tiny residual anastomoses which allow a slow transfusion of blood cells without development of hypovolemia/oligohydramnios in the donor and hypervolemia/polyhydramnios in the recipient.

Table 1: Quintero Staging System for Twin-Twin Transfusion Syndrome (TTTS). Note that the Polyhydramnios-Oligohydramnios Sequence is the Precondition, Present at Every Stage of the Disease

TTTS Stage	Ultrasounds Features
Polyhydramnios-oligohydramnios sequence	
I	Visualization of bladders in both twins
II	Non-visualization of fetal bladder in donor twin
III	Doppler abnormalities (*i.e*. Absent or reversed umbilical artery diastolic flow, reversed ductus venosus a-wave flow, pulsatile umbilical vein flow)
IV	Ascites or hydrops in one or both twins
V	Fetal demise in one or both twins

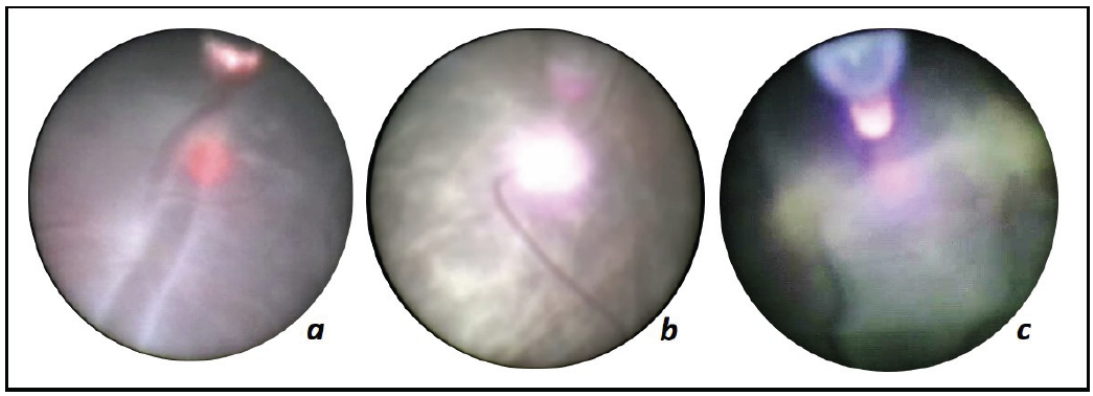

Figure 2: Fetoscopic laser coagulation of placental vascular anastomoses according to the Solomon technique. a) identification of a vascular anastomosis by fetoscopy; b) laser coagulation of the vascular anastomosis; c) linear connection of two contiguous vascular anastomoses.

In order to reduce such occurrence, a new approach named Solomon technique has been conceived and introduced in clinical practice after a multicentric randomized controlled trial [15]. Taking inspiration from the novel of King Solomon, the procedure is performed by drawing a coagulation line from one edge of the placenta to the other connecting any anastomoses identified with the selective procedure, so to obtain a complete dichorionization of the placenta (Figures **2** and **3**) [15].

Even though not reported in the Solomon trial, recent observational studies suggest that performing a coagulation line on the placenta might increase the risks of placental abruption and pPROM [16, 17].

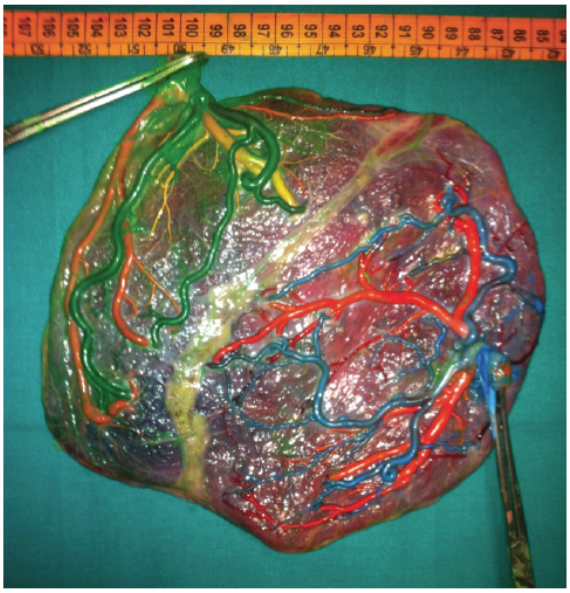

Figure 3: Monochorionic placenta of a pregnancy complicated by twin to twin transfusion syndrome managed by fetoscopic laser therapy. A complete dichorionization according to the Solomon technique can be demonstrated after birth by means of injection study.

A recently published international randomized control trial proved that expectant management rather than immediate surgery is a safe option in stage 1 TTTS in asymptomatic pregnant women [18].

PERINATAL SURVIVAL

Post-operative fetal demise rates, often reported in combination with miscarriage rates without clear-cut separation of the two events, are about 13 to 36%, with some series reporting higher demise rates for donor than recipient twin [19-22].

Neonatal mortality has also significantly decreased during years, from 14%-29% in cases treated with serial AR to 5-8% following treatment with laser coagulation [23].

The improved overall survival is likely the sum of several factors: refinements of fetoscopic instruments and techniques, fetal surgeons learning curve effect, enhanced awareness, diagnosis and referral of TTTS and, last but not least, improved neonatal intensive care.

PERINATAL AND LONG-TERM MORBIDITY

As a consequence of the increased perinatal survival due to improved antenatal treatment strategies, attention is now moving toward short and long-term morbidity in survivors.

A main concern is represented by prematurity which is responsible for a significant portion of morbidity and mortality in TTTS neonates.

Mean gestational age at delivery in treated MC pregnancies is 32 weeks, with the premature rupture of membranes (pPROM) that complicates 25% of cases,

being the main cause of preterm delivery [24]. One of the reasons why preterm birth rates remain high despite improvements in techniques and obstetrical skill is the increasing number of ongoing multifetal pregnancies (with uterine over distension) with a shift of post-operative complications to non-lethal obstetrics complications such as pPROM.

Prematurity-related morbidity includes respiratory distress syndrome, chronic lung disease, retinopathy of prematurity, necrotizing enterocolitis, and cerebral injury, including intraventricular haemorrhage and periventricular leukomalacia [23].

Beyond the burden of prematurity, specific perinatal complications have been described both in ex-recipients and in ex-donors twins after laser therapy, mainly concerning cardiovascular, renal and cerebral morbidity [23, 24].

Cardiovascular Morbidity

TTTS is essentially a cardiovascular disorder and TTTS survivors show a 12-fold increased risk of congenital heart disease (CHD) compared to singletons, and double the normal incidence in non TTTS twins, due to severe hemodynamic instability that can alter cardiac development [25-27].

Recipient twins show the highest incidence of cardiovascular morbidity, which can be transient, or progress and sometimes persist beyond the neonatal period. Cardiovascular manifestations in the recipient twin include fetal and neonatal hypertension, persistent pulmonary hypertension of the neonate, tricuspid and, rarely, mitral regurgitation, left chamber myocardial infarction, pulmonary artery calcification and right ventricular outflow tract obstruction (RVOTO) [27]. It has been speculated that recipient twin cardiomyopathy could be the consequence of both the excess of blood volume, through the placental anastomoses responsible for TTTS, and the passage, from donor to recipient, of vasoactive peptides such as endothelin-1, renin and angiotensin II, that increase vascular resistance: the result is a rise in both preload and afterload on the heart of the recipient.

Right ventricular outflow tract anomalies as pulmonary stenosis, atresia and insufficiency may develop in about 10% of recipients. They are usually diagnosed at the time of TTTS occurrence, but some cases arise only after laser surgery or even in the postnatal period. In a large prospective cohort study on MCDA twin pregnancies complicated by TTTS published in 2018, the incidence of postnatal RVOTO was 2.1-4%, and the worth of a promptly diagnosis was stressed due to the risk of progression to severe RVOTO with the need for intervention in infancy [28].

Fetoscopic laser surgery, by interrupting the passage of blood and vasoactive mediators, ensures cardiovascular improvement in affected recipient twins [25]. Indeed, resolution of functional obstructions (*e.g*. functional pulmonary atresia) are largely reported after fetoscopic laser treatment, with a postnatal prevalence of RVOTO around 3.5% [25].

However, these cardiac abnormalities may persist after successful laser treatment if the myocardial tissue has already been damaged by persistent overload. The main risk factor for persistence of RVOTO in the postnatal period seems to be early onset of TTTS, possibly due to a greater vulnerability of the immature fetal heart to haemodynamic imbalances and endothelial damage, which eventually lead to persistent valve dysplasia [28].

In selected cases, pulmonary stenosis may be so severe that balloon valvuloplasty is required after birth.

Donor twins are not spared from the risk of CHD since an increased risk for aortic coarctation has been reported [29]. The narrowing of the aortic arch may develop secondary to reduced blood flow caused by the decreased left-sided cardiac output due to hypovolemia.

Moreover, donor twins result at increased risk for hypertension since chronic renal under-perfusion, alteration in vascular stiffness, prematurity and low birth weight are all risk factors for hypertension [26].

Given the increased prevalence of congenital heart disease in TTTS survivors, intra-uterine surveillance as well as careful post-natal cardiac assessment and follow-up for both twins are warranted.

Available data on long-term outcomes based on small series by the age of 10 years seem reassuring, and show no significant myocardial dysfunction in either twin even when a severe myocardial dysfunction was evident antenatally [26].

Renal Function in Donor Twin

Donor twins are at increased risk of renal impaired function caused by prolonged and severe hypovolemia and oligo-anuria. Early studies on TTTS not treated with laser surgery reported significant rates of renal

complications including renal cortical necrosis and fibrosis, hematuria, temporary renal insufficiency, acute renal failure needing long-term peritoneal dialysis, or permanent tubular dysfunction with polyuria due to renal tubular dysgenesis [30-32].

Following the introduction of fetoscopic laser surgery, the incidence of short-term renal dysfunction has been proved to be low, particularly after complete surgery [32]. Hence, evidences suggest that laser treatment can preserve kidney function in the surviving twin by re-establishing a normal circulating volume.

However, the evaluation of long-term renal function in large cohorts of TTTS twins treated by laser therapy is lacking, and no assumptions can be made on the real protective effect after the initial neonatal period. For this reason, a careful investigation and follow-up of renal function should be offered in donor twins who survived after TTTS.

Cerebral Injury

The sudden hemodynamic changes in TTTS can cause profound disturbances of brain perfusion that threaten normal brain development in MC fetuses. Both ischaemic and haemorrhagic cerebral injuries can take place in twins experiencing TTTS [33, 34]. Fetoscopic laser coagulation of placental anastomoses proved to reduce the incidence of cerebral injuries at birth compared to sole amnioreduction and to untreated cases [35]. Nonetheless, a correlation between acquired cerebral lesions and both the severity of the disease and the laser procedure itself (likely due to abrupt changes in hemodynamics) has been advocated [35]. A large case-control study comparing the incidence of cerebral injury detected by neonatal cranial ultrasound in 267 monochorionic neonates after TTTS treated by laser therapy and 267 gestational age matched dichorionic neonates showed similar incidence of severe cerebral lesions (8.6% in MC and 6.7% in DC neonates respectively, p =0.44) [36]. At multivariate regression analysis, only gestational age at delivery resulted as independent risk factor for severe cerebral lesions (OR 1.35 for each week less, 95% CI 1.14 –1.59; p<0.01). Interestingly, cerebral injuries in twins with TTTS most often occurred antenatally [36].

Several types of brain lesions have been described, such as intraventricular hemorrhage, periventricular leukomalacia, post-haemorrhagic ventricular dilation, cerebral atrophy, porencephalic cysts and ischemic stroke [36]. These lesions can be detected by prenatal and neonatal ultrasounds or magnetic resonance imaging, with a reported incidence between 3 and 16% [37].

De novo fetal cerebral lesions following laser treatment are documented in approximately 2% of fetuses (equally in donors and recipients) and are mainly associated with incomplete surgery and subsequent recurrence of TTTS or post laser TAPS [38].

As further discussed below, these acquired lesions may play a central role for subsequent long-term neuromorbidity.

Long Term Neurodevelopmental Outcome

For both twins, long-term morbidity is mainly related to the neurological outcome.

Data from neurodevelopmental follow-up studies are tricky to summarize since there is a variety of test instruments employed by different research groups and a clear differentiation between severe and minor neurodevelopmental impairment (NDI) is often lacking.

Minor neurocognitive impairments concern defective cognitive abilities, academic performance, communication or fine motor function as well as behavioural disorders, and have been reported in up to 30% of TTTS survivors [21]. Studies on mild NDI are scants and hindered by methodological heterogeneity and loss at follow up, since larger time-periods are needed to evaluate subtle neurodevelopmental aspects that sometimes only manifest beyond school-age. Even though ‘minor’ this type of disabilities can have a substantial impact on the care, costs and the emotional and educational needs of children.

Major NDI can be defined as cerebral palsy (CP), severe motor skills delay or cognitive developmental delay, bilateral blindness, or deafness [24]. In TTTS survivors managed by serial amnioreduction, major NDI ranged from 14% to 26%, with a 14% of CP rate (range 5%–23%), while fetoscopic laser surgery greatly decreased the incidence of both cerebral injury and NDI [11, 12, 33, 35]. Long-term follow up studies derived by the most recent laser therapy series seem to show a decreasing trend in the incidence of severe neurological abnormalities, with overall rates between 3 and 6%, and cerebral palsy rates of 2-3% [24, 39-41].

Factors that might worsen the long-term neurodevelopmental outcome are advanced gestational age at laser treatment, advanced Quintero stage of TTTS, low gestational age at birth, low birth

weight, growth restriction, and cerebral injuries, but according to the last review based on more than 1300 infants aged 2 years, low gestational age at birth is the only variable independently associated with neurodevelopmental impairment, with an odds ratio of 1.33 (95% CI 1.05-1.67, p=0.02) for each week of gestation lost [24, 33, 40-42].

As stated by the same Authors, the neurodevelopmental outcome recorded at 2 years of age show rates of minor impairment of 7-11% and severe impairment of 3-11% and well reflects the subsequent outcome, with an overall incidence of severe NDI in children aged 4–6 years that persists between 4% and 13% (with an incidence of CP of 2–13%) [24].

Sprujit and colleagues have analyzed a large longitudinal cohort study on 434 children evaluated up to 2 years of age, and found that for each 100 grams increase in birth weight there was a 0.41 increase in cognitive scores (95% CI 0.18-0.64, p 0.000) [41]. Importantly, they didn't find a significant association of neither severe prematurity (delivery before 32 weeks of gestational age) nor the presence of cerebral injury with neurodevelopmental impairment at 2 years, warranting routine long-term follow up in all TTTS survivors [41].

Of outstanding importance for understanding the impact of chorionicity, TTTS and antenatal treatment on neurologic morbidity is the comparison among MC twins after TTTS treated with laser and gestational age-matched dichorionic twins.

A recent population-based study comparing the neurodevelopmental outcome up to 10 years of age of MC twins treated by laser therapy with matched DC twins who did not have any invasive intervention during pregnancy showed that the rate of event-free survival, long-term neurodevelopmental and behavioural outcomes (primary outcomes), as well as school career, therapies, or special aid equipment (secondary outcomes) were similar in both groups and that the only predictive factor for event-free survival was gestational age at birth [40].

This and similar studies point at the remarkable portion of long-term neuromorbidity attributable to prematurity in TTTS survivors [12, 21, 40, 42].

Recipient and donor twins appear to have similar risks of NDI. During antenatal life, they are both at risk even if they face different hemodynamic challenges. It can be assumed that donors are at increased risk for hypoperfusion-related ischemic lesions, while recipients face hyperviscosity-related ischemia due to polycythemia as well as hemorrhagic events due to hypertensive hypervolemic overload. A systematic review and meta-analysis of more than 1000 TTTS treated by laser surgery found no differences in neurologic morbidity between donors and recipients (9% vs 10%, p=5.66), even if none of the studies included in the analysis had the donor-recipient comparison as primary outcome [43].

CONCLUSIONS

TTTS represents one of the most lethal conditions in prenatal life.

Since the introduction of fetoscopic laser coagulation of the placental anastomoses responsible for the disease, this condition can be solved within days from its detection, leading to increased, even though still suboptimal, dual twin survival rates compared to a few years ago.

Given the higher pre- and post-natal survivals, the actual great deal is morbidity in fetuses, neonates and children.

Over the last fifteen years, postoperative complications have in truth shifted from miscarriage and intrauterine fetal demise to complications that influence the ongoing pregnancy. PPROM and preterm birth represent the current enemy to face, with its main burden in terms of long-term neurodevelopmental impairment.

The current picture engenders some considerations.

From the antenatal point of view, there is the need for further improving surgical techniques (just to name some hints, by reducing the diameter of the entry port, ameliorating the instruments' flexibility, reducing placental tissue damage linked to the Solomon technique, or effectively plugging the entry hole at the end of fetoscopic surgery), and possibly find a non-invasive surgical approach. Moreover, a main goal for obstetricians should be to improve early screening and prediction of MC pregnancies at risk for developing TTTS. Finally, efforts should be made for enhancing obstetric management of threatened preterm labour in multifetal pregnancies.

From the postnatal perspective, post-discharge surveillance programmes and long-term standardized follow-up into adulthood must become the standard of care, given the long-term health risks concerning TTTS

survivors. Prenatal diagnosis and fetal surgery, as well as neonatal intensive care have the ethical responsibility of providing a decent quality of life in the survivors, and these high-risk pregnancies remain a serious risk factor for neurodevelopmental impairments. Hence, long-term follow-up of these patients is needed to assess the effects of pre- and postnatal interventions and to ensure timely care of late onset health issues.

Finally, the great improvements observed so far strengthen the indication to centralize fetoscopic surgery and neonatal intensive care in specialized high-volume centers with dedicated and experienced multidisciplinary teams.

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